American Journal of Medical Genetics 68:91–93 (1997)

Family With Branchial Arch Anomalies, Hearing Loss, Ear and Commissural Lip Pits, and Rib Anomalies. A New Autosomal Recessive Condition: Branchio-Oto-Costal Syndrome?

Maurizio Clementi*, Isabella Mammi, and Romano Tenconi
Servizio di Genetica Medica, Dipartimento di Pediatria, Università di Padova, Italy

We report on a family in which 3 sibs were affected with conductive deafness, bilateral preauricular and commissural lip pits, monolateral branchial fistula, and rib anomalies. On the basis of parental consanguinity, lack of clinical variability and affected subjects of both sexes, this condition seems to be inherited as an autosomal recessive trait. We suggest that these findings comprise a new autosomal recessive entity of branchial, auricular and costal anomalies, for which we suggest the acronym BOC (branchio-oto-costal) syndrome. Am. J. Med. Genet. 68:91–93, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: lip pits; branchial arch; costal anomalies; branchio-oto-costal syndrome

INTRODUCTION

We describe a family with 3 sibs born to consanguineous parents presenting bilateral conductive deafness, bilateral preauricular and commissural lip pits, lateral cervical sinuses and rib anomalies. This association has not been reported previously and may represent a new syndrome: the branchio-oto-costal (BOC) syndrome.

CLINICAL REPORT

Family History

The propositus was a self-referred 43-year-old man. In 1965, his family underwent otorhinolaryngologic (ORL) evaluation because his 2 sibs and he had hearing loss and branchial fistulas. At that time, his mother and father, 49 and 57 years old, respectively, were apparently normal; in particular, no preauricular and mouth pits, nor cervical sinuses were observed, and hearing function was normal. However, their renal morphology and function were not evaluated. An older brother and sister were found to have similar findings as the propositus.

This family was reported subsequently as a case of familial minor auricular dysplasia associated with cervical facial anomalies [Faggian, 1967]. At that time, parental consanguinity was denied, and when the propositus underwent genetic counseling, he also denied any parental consanguinity, despite an identical ancestral family name. However, the observation of a similar phenotype in the 3 sibs caused us to request further information on the parents' origins. A search of church files by the propositus disclosed that the parents were second cousins.

Because the propositus' parents and 2 sibs refused to be examined, we obtained information about the family from the propositus, and from the published data [Faggian, 1967].

Patient 1

The propositus was delivered vaginally at term following a normal pregnancy and labor. Psychomotor and language development were normal. He followed a regular course of study and obtained a professional diploma. He was found fit for military service, and no signs of disease were noted. He is now working as a wood carver and is unmarried. On physical examination at 43 years weight (62 kg, 25–50th centile), height (169 cm, 10–25th centile) and head circumference (55.5 cm) were normal. The ocular region was normal, with an outer and inner canthal distance of 8.5 (25th centile) and 3.0 cm (50th centile) respectively. Auricles were normal in shape and length (6.5 cm bilaterally, 75th centile); a bilateral preauricular pit was observed. When he opened his mouth (Fig. 1) bilateral commissural lip pits were evident together with a very narrow palate, crowded teeth, and morsus inversus. A nondraining branchial fistula was present on the median border of the left sternocleidomastoid muscle. Cardiovascular, pulmonary, abdominal and genital findings were normal. Limbs were normal except for a mild

*Correspondence to: Maurizio Clementi, M.D., Servizio di Genetica Medica, Dipartimento di Pediatria, Via Giustiniani, 3, 35128 Padova, Italy.

Received 3 October 1995; Accepted 2 February 1996

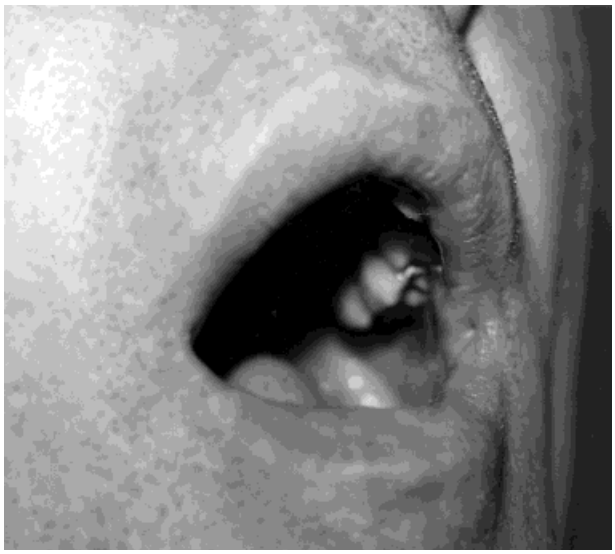

Fig. 1. Patient 1: Commissural lip pits.

difference in leg length (left 1 cm longer than right) and the traumatic absence of two phalanges of the 5th left finger. Neurologic findings were normal.

ORL evaluation in 1965 demonstrated normal hearing function, but an audiometric examination at the age of 42 years detected bilateral sensorineural hearing loss (40–50 dB at low frequencies; 60 dB at high frequencies).

Renal function was normal and ultrasonography showed normal kidney and collecting system anatomy. Findings of a complete ophthalmological evaluation at 43 years were normal. A chest roentgenograph (Fig. 2) was performed because of the presence of rib anomalies in the sibs, and showed hypoplasia of first and third ribs bilaterally, and fifth left rib, with absent ossification of the posterolateral segments of the first ribs and of lateral segments of third and fifth hypoplastic ribs.

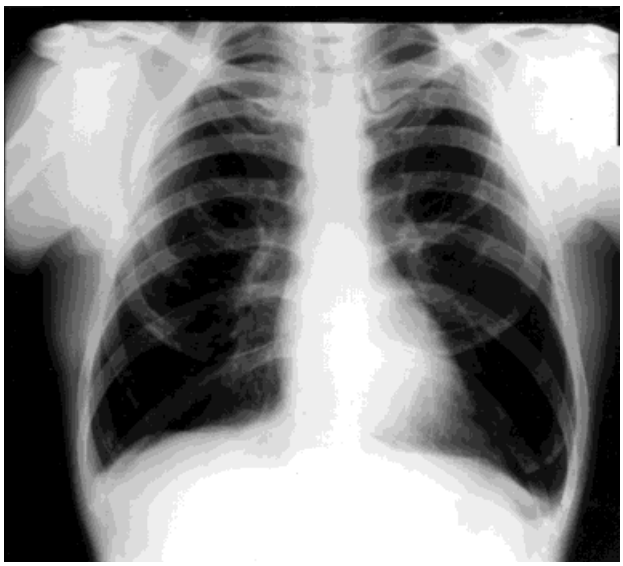

Fig. 2. Patient 1: Costal anomalies (see text).

Irregular anterolateral calcifications normal for age were also noted. The hypoplastic first rib was fused to the manubrium.

Patient 2

This 52-year-old woman is the firstborn in the sibship and was delivered vaginally at term. Physical and psychomotor development were normal, but language development was delayed due to dyslalia and rhinolalia aperta. She showed a progressive conductive hearing loss for which she has worn hearing aids since the age of 20. She attended an institute for speech therapy up to the age of 15. She now works in a clothing factory; she is married to a healthy man and they decided not to have children.

At 22 years, she underwent surgical repair of a right lateral cervical fistula that drained saliva during meals. At that time, examination also showed bilateral preauricular and commissural lip pits, a cupped right ear, and very narrow palate. Roentgenographic examination following the injection of contrast medium into the lateral cervical defect showed a narrow 3-cm-long canal that almost reached the lateral right horn of the hyoid bone. Chest roentgenograph demonstrated bilateral hypoplasia of the first and second ribs.

She also underwent surgical explorative tympanotomy of the right ear that showed "ivory-like ossicles, with footplate appearing like a marble block, in which neither the annular ligament nor the oval window edging are distinguishable" [Faggian, 1967]. Audiometric examination at that time confirmed the bilateral conductive hearing loss (50 dB at all frequencies) with complete absence of stapedial reflexes at impedance audiometry. Renal function at the age of 52 years was normal, as was renal and collecting system anatomy on ultrasonography.

Patient 3

This 50-year-old man is the secondborn sib. He was delivered vaginally at term after an uneventful pregnancy. Psychomotor development was normal; language development was delayed due to dyslalia and rhinolalia aperta.

Like his brother and sister, he also presented bilateral preauricular and commissural lip pits, a highly arched palate, cleft soft palate, crowded teeth and a right cervical fistula which occassionally drained. Roentgenographic examination after the injection of contrast medium into the lateral cervical defect showed a long tubular sinus that reached to the lower end of the tonsillar fossa. Audiometric examination disclosed a bilateral conductive hearing loss (60 dB at all frequencies) with complete absence of stapedial reflexes at impedance audiometry. Chest roentgenograph showed bilateral hypoplasia of the first and second ribs. Renal ultrasonography and renal function evaluation were not performed.

DISCUSSION

A combination of developmental anomalies of first and second branchial arch structures occurs in several

malformation syndromes. Among these, the branchio-oto-renal syndrome (BOR syndrome, MIM*113650) is the most frequent, well-known and documented. The branchio-oto (BO) and branchio-oto-ureteral (BOU) syndromes probably should also be included in this term, as they are considered an expression of phenotypic variability of the same entity [Gorlin et al., 1990]. This hypothesis was advanced based on the observation of familial cases, in which both BOR and BO, or BOR and BOU syndromes were present in different members of the same family [Hunter, 1974; Rowley, 1969; Fraser et al., 1978], and the occurrence of ureteral anomalies in a patient with BOR syndrome.

Many other syndromes, in which branchial arch anomalies are present without renal involvement, have been described: oto-facio-cervical syndrome (MIM 166780); branchial cysts, sinuses, fistulas or tags as isolated defects (MIM *113600); preauricular pits or sinuses as isolated findings [Gorlin et al., 1990], and preauricular pits and hearing loss with or without malformed auricles [Gorlin et al., 1990]. Like the BOR syndrome, all these syndromes have an autosomal dominant mode of inheritance; the BOR syndrome also has variable expression and very high, although probably incomplete penetrance.

Distinctive findings in the branchial-oculo-facial (BOF) syndrome [Lin et al., 1992; McCool and Weaver, 1994] are branchial fistulas (90% of patients) or supra-auricular defects with abnormal overlying skin (atrophic skin lesions, linear aplasia cutis, scarring), while discrete branchial pits, cysts and fistulae are not present. Cleft lip or pseudocleft are found in 90%, and major or minor ocular defects occur in at least 78% of the patients. Conductive hearing loss is a frequent finding (71%). Major skeletal defects have not been detected, and in particular costal anomalies have never been described in the BOF syndrome [Lin et al., 1995].

The oto-facio-cervical syndrome has been described in only two families [Fara et al., 1967; Dallapiccola and Mingarelli, 1995], in which the affected subjects presented hearing loss and preauricular fistulas with lateral cervical fistulas occurring in some. Cervical anomalies consisted of sloping shoulders, low-set clavicles and winged scapulae. No costal anomalies were observed.

Our patients have conductive deafness, bilateral preauricular and commissural lip pits, monolateral branchial fistula, and rib anomalies. Sensorineural instead of conductive deafness was present in patient 1. All sibs have a very narrow and arched palate, but only patient 3 had a cleft soft palate. Based on the absence of ocular and renal abnormalities, and the presence of costal anomalies and mouth angle pits, we think that a diagnosis of BOR or BOF syndromes is very unlikely. Moreover, the commissural lip pits which were observed in all sibs, could be distinctive of this syndrome. Indeed, although this finding is not rare (prevalence of 1500 in the general population), it has no clinical relevance and it is not reported to be associated with other anomalies. In most cases it is sporadic, and only rarely inherited as a dominant trait [Lettieri, 1993]. On the basis of parental consanguinity, lack of clinical variability and affected subjects of both sexes, this condition seems to be inherited as an autosomal recessive trait, unlike the above mentioned conditions.

These findings appears to constitute a new autosomal recessive entity, characterized by branchial, auricular and costal anomalies for which we propose the acronym BOC (branchio-oto-costal) syndrome.

REFERENCES

Dallapiccola B, Mingarelli R (1995): Otofaciocervical syndrome: A sporadic patient supports splitting from the branchio-oto-renal syndrome. J Med Genet 32:816–818.

Faggian I (1967): Considerazioni patogenetiche sulle piccole displasie auricolari associate ad anomalie cervico-facciali. Bollettino delle malatti dell'orecchio, della gola, del naso. I semestre, pp 144–162.

Fara M, Chlupackova V, Hrivrakova J (1967): Dismorfia oto-facio-cervicalis familiaris. Acta Chir Plast 9:255–268.

Fraser FC, Ling D, Clogg D, Nogrady B (1978): Genetic aspects of the BOR syndrome-branchial fistulas, ear pits, hearing loss, and renal anomalies. Am J Med Genet 2:241–252.

Gorlin RJ, Cohen MM Jr, Levin LS (1990): "Syndromes of the Head and Neck." Third edition. New York: Oxford University Press, pp. 657–659.

Hunter AGW (1974): Inheritance of branchial sinuses and preauricular fistulae. Teratology 9:225–228.

Lettieri J (1993): Lip pits. In: Stevenson RE, Hall JC, Goodman RM (eds): "Human Malformations and Related Anomalies." Vol. II. New York: Oxford University Press, pp 380–381.

Lin AE, Doherty R, Lea D (1992): Branchio-oculo-facial and branchio-oto-renal syndromes are distinct entities. Clin Genet 41:222–223.

Lin AE, Gorlin RJ, Lurie IW, Brunner HG, Van der Burgt I, Naumchik IV, Rumyantseva NV, Stengel-Rutkowski S, Rosenbaum K, Meinecke P, Muller D (1995): Further delineation of the branchio-oculo-facial syndrome. Am J Med Genet 56:42–59.

McCool M, Weaver DD (1994): Branchio-oculo-facial syndrome: Broadening the spectrum. Am J Med Genet 49:414–421.

Rowley PT (1969): Familial hearing loss associated with branchial fistulas. Pediatrics 44:978–985.